4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2016-D-0271]

Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a revised draft guidance for industry entitled "Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act" ("revised draft guidance"). This revised draft guidance, when finalized, will describe how FDA intends to apply certain provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to human drug products compounded by State-licensed pharmacies that are not outsourcing facilities and distributed for use within a hospital or health system. First, it addresses the requirement that compounding be based on the receipt of a valid prescription order for an identified individual patient. Second, it addresses the provision concerning compounded drug products that are essentially copies of a commercially available drug product. This draft guidance revises the draft guidance issued in 2016 entitled, "Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act" ("draft guidance"). FDA is revising the draft guidance to address stakeholder feedback and provide further clarification on policies regarding hospital and health system compounding. This revised draft guidance is not final nor is it in effect at this time.

DATES: Submit either electronic or written comments on the revised draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this revised draft guidance before it begins work on the final version of the guidance. Submit electronic or written comments on the

proposed collection of information in the revised draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF THE PUBLICATION OF THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2016-D-0271 for "Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the

prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of this revised draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your request or include a fax number to which the revised draft guidance may be sent. See the SUPPLEMENTARY INFORMATION section for information on electronic access to the revised draft guidance.

FOR FURTHER INFORMATION CONTACT:

With regard to the revised draft guidance: Tracy Rupp, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Silver Spring, MD 20993, 301-796-3100.

With regard to the proposed collection of information: Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-5733, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a revised draft guidance for industry entitled "Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act." Pharmacies located within a hospital, or standalone pharmacies that are part of a health system, frequently provide compounded drug products for administration within the hospital or health system. Some of these compounders seek to compound under section 503A of the FD&C Act (21 U.S.C. 353a) and others have registered with FDA as outsourcing facilities and are subject to section 503B of the FD&C Act (21 U.S.C. 353b).

Section 503A of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to be exempt from the following three sections of the FD&C Act:

- Section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) requirements);
- Section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and
- Section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications).

This revised draft guidance proposes policies for FDA's application of certain provisions of section 503A of the FD&C Act to human drug products compounded by State-licensed pharmacies that are not outsourcing facilities and distributed for use within a hospital or health system. First, the revised draft guidance addresses the requirement that compounding be based on the receipt of a valid prescription order for an identified individual patient. Second, it addresses the provision concerning compounded drug products that are essentially copies of a commercially available drug product. This revised draft guidance does not apply to human drug products compounded by outsourcing facilities under section 503B of the FD&C Act, compounded drug products that are not distributed for use within a hospital or health system, or drug products compounded for use in animals.

In the *Federal Register* of April 18, 2016 (81 FR 22610), FDA announced the availability of a draft guidance for industry entitled, "Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act" ("draft guidance"). The draft guidance proposed new policies for the application of section 503A of the FD&C Act to drug products compounded by licensed pharmacists or physicians in State-licensed hospital or health system pharmacies. In particular, the draft guidance described certain circumstances under which FDA generally would

not intend to take action if a hospital or health system pharmacy distributed compounded drug products without first receiving a patient-specific prescription or order.

The comment period on the initial draft guidance ended on July 18, 2016. FDA received approximately 76 comments on the draft guidance. FDA is issuing a revised draft guidance with certain changes made in response to received comments or on its own initiative. For example, the prescription requirement enforcement policy described in the revised draft guidance does not consider whether the drug products are distributed only to healthcare facilities that are located within a 1-mile radius of the compounding pharmacy ("1-mile radius policy"). Instead, the Agency is proposing a two-part, risk-based compliance policy.

In addition, the revised draft guidance proposes new policies for hospital and health system pharmacies regarding the provision in section 503A of the FD&C Act which states that to qualify for the exemptions under section 503A of the FD&C Act, among other conditions, a drug product must be compounded by a licensed pharmacist or physician who does not compound regularly or in inordinate amounts any drug products that are essentially copies of a commercially available drug product.

FDA is issuing this revised draft guidance to address stakeholders' feedback, reflect additional Agency consideration of the proposed policies, and enable the public to further review and comment before finalization.

This revised draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The revised draft guidance, when finalized, will represent the current thinking of FDA on "Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

Under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal Agencies to provide a 60-day notice in the *Federal Register* concerning each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document. We are consolidating the information collection in the revised draft guidance with the information collections and approvals under OMB control number 0910-0800.

With respect to the following collection of information, FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Human Drug Compounding Under Sections 503A and 503B the Federal Food, Drug, and Cosmetic Act

OMB Control Number 0910-0800--Revision

This notice solicits comments on certain information collections found in the revised draft guidance entitled "Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act" ("revised draft guidance"). This guidance, when finalized, will support implementation of the copies provisions of the 1997 Food and Drug

Administration Modernization Act (FDAMA) (Pub. L. 105-115) discussed in section 503A of the FD&C Act, which were maintained by the 2013 Drug Quality and Security Act (DQSA) (Title I of Pub. L. 113-54).

For efficiency of Agency operations, we are revising OMB control number 0910-0800 to include information collections relating to the copies policies for hospital and health system pharmacies that are not outsourcing facilities, as proposed in the revised draft guidance document.

As proposed in section III.B of the revised draft guidance, among other conditions, we generally would not intend to take action against a hospital or health system pharmacy that is not an outsourcing facility for compounding a drug product regularly or in inordinate amounts that is essentially a copy of a commercially available drug product, if the compounded drug product is administered only to patients within the hospital or health system and the pharmacy obtains from the prescriber a statement that: (1) specifies a change between the compounded drug product and the commercially available drug product; (2) indicates that the compounded drug product will be administered only to patients for whom the change produces a significant difference from the commercially available drug product; and (3) describes the intended patient population for the compounded drug product. In addition, the revised draft guidance specifies that the statement would be maintained in the hospital or health system pharmacy to address routine orders for patients for whom the change produces a significant difference, and a statement would be on file for each prescriber that covers each drug product that is compounded.

As provided in section III.B of the revised draft guidance, except for the policy proposed above regarding the documentation of a prescriber's determination of significant difference, we propose to apply the policies described in the guidance, "Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act" ("503A copies guidance") to drug products compounded by hospital and health system pharmacies that are not outsourcing facilities.

As described in section III.B.2 of the 503A copies guidance, and proposed in the revised draft guidance to apply to hospital and health system pharmacies, if a compounder intends to rely on a prescriber determination of significant difference to establish that a compounded drug is not essentially a copy of a commercially available drug product, the compounder should ensure that the determination is documented on the prescription. If a prescription does not make clear that the prescriber made the determination required by section 503A(b)(2) of the FD&C Act, or a compounded drug is substituted for the commercially available drug product, the compounder can contact the prescriber and if the prescriber confirms it, make a notation on the prescription that the compounded drug product contains a change that makes a significant difference for the patient. The notations should be as specific as those described in the 503A copies guidance, and the date of the conversation with the prescriber should be included on the prescription.

With respect to the determination of significant difference described above, we estimate that, annually, a total of approximately 3,075 hospital or health system pharmacies (table 1) will obtain a prescriber determination of significant difference. This estimate represents approximately half of the hospitals in the United States, including those that are in health systems. Of these, we estimate that approximately half (1,538) will have hospital or health system pharmacies that will follow the policy in the revised draft guidance, obtaining a statement of significant difference for the intended patient population, and approximately half (1,537) will have hospital or health system pharmacies that will follow the policy with respect to prescriber determination of significant difference in the 503A copies guidance, documenting the notation on the individual patient prescription. This estimate assumes that most pharmacies in smaller hospitals and health systems will follow the policy in the 503A copies guidance because a prescriber determination of significant difference will not be routinely needed and can be most efficiently managed on a patient-by-patient basis. On the other hand, this estimate assumes that most pharmacies in larger hospitals and health systems will follow the policy in the revised draft guidance because the need for a prescriber determination of significant difference is more

routinely necessary and, therefore, most efficiently managed with a statement of significant difference that is maintained in the hospital or health system pharmacy to address routine orders for patients for whom the change produces a significant difference.

We estimate that, annually, approximately 1,538 hospital or health system pharmacies following the policy in the revised draft guidance will obtain approximately 30 statements of significant difference for compounded drug products, for a total of approximately 46,140 statements (table 1, row 1). We estimate that the consultation between the hospital or health system pharmacy and the prescriber to obtain the statement of significant difference will require approximately 5 minutes per statement (table 1, row 1).

We estimate that, annually, approximately 1,537 hospital or health pharmacies following the policy in the 503A copies guidance will consult a prescriber to determine whether the prescriber has made a determination that the compounded drug product has a change that produces a significant difference for a patient as compared to the comparable commercially available drug and that the compounders will document this determination on approximately 76,850 prescription orders for compounded drug products (table 1, row 2). We estimate that the consultation between the compounder and the prescriber and adding a notation to each prescription that does not already document this determination will take approximately 3 minutes per prescription order (table 1, row 2). The average burden per consultation and notation for pharmacies following the significant difference policy in the 503A copies guidance, compared to pharmacies following the significant difference policy in the revised draft guidance, is estimated to be less (3 minutes) because the significant difference determination described in the 503A copies policy is specific to one patient, whereas the statement of significant difference in the revised draft guidance describes the intended patient population.

In addition, as described in section III.B.3 of the 503A copies guidance, and proposed in the revised draft guidance to apply to hospital and health system pharmacies, if the drug product was compounded because the approved drug product was not commercially available because it

was on the FDA drug shortage list, the prescription or a notation on the prescription should note that it was on the drug shortage list and note the date the list was checked. We estimate that a total of approximately 4,613 hospital or health system pharmacies will document this information on approximately 922,600 prescription orders for compounded drug products (table 1, row 3). We estimate that checking FDA's drug shortage list and documenting this information will require approximately 2 minutes per prescription order (table 1, row 3).

With respect to maintaining records of the statement of significant difference proposed in section III.B of the revised draft guidance, we estimate that a total of approximately 1,538 hospital or health system pharmacies will maintain approximately 46,140 statements of significant difference (table 2, row 1). We estimate that maintaining the records will require approximately 2 minutes per record (table 2, row 1). With respect to maintaining records of the significant difference determination, as provided in section III.B.5 of the 503A copies guidance, we estimate that a total of approximately 1,537 hospital or health system pharmacies will maintain approximately 76,850 records (table 2, row 2). We estimate that maintaining records will require approximately 2 minutes per record (table 2, row 2).

Also with respect to maintenance of records, as described in section III.B.5 of the 503A copies guidance, and proposed in the revised draft guidance to apply to hospital and health system pharmacies, compounders under section 503A should maintain records of (1) the frequency in which they have compounded drug products that are essentially copies of commercially available drug products and (2) the number of prescriptions that they have filled for compounded drug products that are essentially copies of commercially available drug products. We estimate that a total of approximately 3,075 hospital or health system pharmacies will maintain approximately 61,500 records of prescriptions that they have filled for compounded drug products that are essentially copies of commercially available drug products (table 2, row 3). We estimate that maintaining the records will require approximately 2 minutes per record (table 2, row 3).

We estimate the burden of this collection of information as follows:

Table 1.--Estimated Annual Third-Party Disclosure Burden[1]

Activity	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
Consultation between the hospital or health system pharmacy and the prescriber to document the statement of significant difference (revised draft guidance)	1,538	30	46,140	.08 (5 minutes)	3,691
Consultation between the hospital or health system pharmacy and prescriber and the notation on the prescription documenting the prescriber's determination of significant difference (503A copies guidance)	1,537	50	76,850	.05 (3 minutes)	3,843
Hospital or health system pharmacy checking FDA's drug shortage list and documenting on the prescription that the drug is in shortage (503A copies guidance)	4,613	200	922,600	.03 (2 minutes)	27,678
Total					35,212

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 2.--Estimated Annual Recordkeeping Burden[1]

Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
Records of the statement of significant difference (revised draft guidance)	1,538	30	46,140	.03 (2 minutes)	1,384
Records of documentation of significant difference (503A copies guidance)	1,537	50	76,850	.03 (2 minutes)	2,306
Records of frequency and number of prescriptions filled for compounded drug products that are essentially a copy (503A copies guidance)	3,075	20	61,500	.03 (2 minutes)	1,845
Total					5,535

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

IV. Electronic Access

Persons with access to the internet may obtain an electronic version of the revised draft guidance at either https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or https://www.regulations.gov.

Dated: October 4, 2021.

Lauren K. Roth,

Associate Commissioner for Policy.

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